Trastuzumab emtansine – Kadcyla®

Indication

Treatment of HER2 positive unresectable locally advanced or metastatic breast cancer for patients who have previously received a taxane and trastuzumab (Herceptin®).

Patients should have received prior therapy for locally advanced or metastatic disease OR have relapsed within 6 months of completing adjuvant therapy.

Funding needs to be approved prior to commencing treatment.

ICD-10 codes

Codes pre-fixed with C50.

Regimen details

Day	Drug	Dose	Route
1	Kadcyla ®	3.6mg/kg	IV infusion

In order to reduce the risk of medication errors it is recommended that all trastuzumab products are referred to by brand name, i.e. **Kadcyla** (trastuzumab emtansine).

Cycle frequency

21 days

Number of cycles

Until disease progression or unacceptable toxicity.

Administration

Kadcyla is administered in 250mL sodium chloride 0.9% non-PVC infusion bag with a 0.22 micron in-line filter. The first dose is administered over 90 minutes and patients should be observed for infusion related reactions for 90 minutes following completion of the infusion.

If the previous infusion was well tolerated, subsequent doses may be administered over 30 minutes. Patients should be observed for at least 30 minutes following completion of the infusion.

In the event of infusion related reactions, the infusion rate should be slowed or discontinued in severe or life threatening cases.

Pre-medication

Nil

Emetogenicity

This regimen has mild emetic potential.

Additional supportive medication

Antiemetics as per local policy.
H_2 antagonist or PPI, if required, as per local policy.
Mouthwashes as per local policy.
Loperamide if required

Extravasation

Kadcyla is neutral (Group 1)

Investigations – pre first cycle

Investigation	**Validity period** (or as per local policy)
FBC	14 days
U+E (including creatinine)	14 days
LFTs	14 days
Blood pressure	14 days
ECG	Baseline
Echocardiogram	Baseline

Low potassium should be corrected prior to commencing treatment.

If BP ≥ 140/90 mmHg, this should be controlled and managed by the GP prior to commencing treatment.

Investigations – pre subsequent cycles

Investigation	**Validity period** (or as per local policy)
FBC	96 hours
U+E (including creatinine)	7 days
LFTs	7 days
Blood pressure	Baseline then 3 monthly or as clinically indicated
Echocardiogram	Every 3 months

Standard limits for administration to go ahead

If blood results not within range, authorisation to administer **must** be given by prescriber/ consultant

Investigation	**Limit**
Neutrophils	≥ 1.5 x 10^9/L
Platelets	≥ 75 x 10^9/L
Creatinine clearance (CrCl)	≥ 30mL/min
Bilirubin	< 1.5 x ULN
AST/ALT	< 2.5 x ULN
LVEF	> LLN

Kadcycla has not been studied in patients with platelets < 100 x 10^9/L prior to initiation of treatment. If platelets < 50 x 10^9/L kadcyla should be withheld until > 75 x 10^9/L.

Dose modifications

Dose reduction level	**Dose**
Full dose	3.6mg/kg
1st dose reduction	3mg/kg
2nd dose reduction	2.4mg/kg

If more than 2 dose reductions are required treatment should be discontinued.

Doses should **not** be re-escalated following a dose reduction.

- **Haematological toxicity**

If neutrophils < 1.5 x 10^9/L and/or platelets < 75x 10^9/L, delay until recovery.

Platelets (x 10^9/L)	**Action**
25-75	Withhold until ≥ 75 x 10^9/L Continue at same dose
< 25	Withhold until ≥ 75 x 10^9/L Reduce dose by 1 dose level If platelet count < 25 x 10^9 /L for a second time, do not administer until platelet count recovered to ≥ 75 x 10^9 /L and dose reduce to 2.4mg/kg. If platelet count < 25 x 10^9 /L for the third time, discontinue treatment.

- **Renal impairment**

There have been no studies in patients with renal impairment. If CrCl < 30mL/min, consultant decision and close monitoring required.

- **Hepatic impairment**

Kadcyla should not be started if AST/ALT > 2.5 x ULN or bilirubin > 1.5 x ULN prior to initiating treatment.

No adjustment to the starting dose is required for patients with mild or moderate hepatic impairment. Kadcyla has not been studied in patients with severe hepatic impairment.

Kadcyla should be discontinued if AST/ALT > 3 x ULN AND bilirubin > 2 x ULN.

- **Other toxicities**

Left ventricular dysfunction

LVEF must be above LLN for treatment to go ahead. The summary of product characteristics for Kadcyla states that cardiac monitoring is required every 3 months. If the patient has no increased risk of cardiac toxicity and is established on treatment for >9months it may be appropriate to reduce monitoring to every 4-6 months (discuss with consultant).

LVEF	**Kadcycla**
> LLN	Continue
40-LLN and decrease < 10% from baseline **and** asymptomatic	Continue. If BP and renal function adequate start an ACE inhibitor (eg ramipril 2.5mg) and consider a beta blocker (eg bisoprolol 2.5mg). Repeat LVEF within 3 weeks
40-LNN and decrease ≥ 10% from baseline **and** asymptomatic	Withhold. If BP and renal function adequate start an ACE inhibitor (eg ramipril 2.5mg) and consider a beta blocker (eg bisoprolol 2.5mg). Repeat LVEF within 3 weeks and if not within 10% from baseline withhold treatment. Discuss with consultant and refer to cardiology
< 40%	Withhold. If BP and renal function adequate start an ACE inhibitor (eg ramipril 2.5mg) and consider a beta blocker (eg bisoprolol 2.5mg). Repeat LVEF within 3 weeks and if < 40% withhold treatment and discuss with consultant. Refer to cardiology
Symptomatic congestive heart failure	Discontinue

Peripheral neuropathy

If grade 3-4 withhold until ≤ grade 2. Consider dose reduction and monitor.

Pulmonary toxicity

Cases of interstitial lung disease (ILD), including pneumonitis, some leading to acute respiratory distress syndrome

or a fatal outcome, have been reported. Signs and symptoms include dyspnoea, cough, fatigue, and pulmonary infiltrates. If ILD is suspected, withhold treatment until excluded. If ILD diagnosed Kadcyla should be discontinued.

Adverse effects - for full details consult product literature/ reference texts

- **Rare or serious side effects**

Myelosuppression
Cardiotoxicity
Haemorrhage
Hepatobiliary disorders
Neurotoxicity
ILD, Pneumonitis

- **Frequently occurring side effects**

Myelosuppression
Raised transaminases
Infusion related reactions
Hypokalaemia
Stomatitis
Diarrhoea
Musculoskeletal pain
Dyspnoea
Fatigue
Peripheral neuropathy

- **Other side effects**

Insomnia
Headaches, dizziness
Rash
Arthralgia, Myalgia

Significant drug interactions – for full details consult product literature/ reference texts

Warfarin/coumarin anticoagulants: increased or fluctuating anticoagulant effects. Avoid if possible, consider switching patient to a low molecular weight heparin during treatment or if the patient continues taking an oral anticoagulant monitor the INR at least once a week and adjust dose accordingly.

CYP24A inhibitors: (ketoconazole, itraconazole, clarithromycin, atazanivir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, and voriconazole): avoid concomitant administration – increased risk of toxicity.

Additional comments

Women of childbearing potential should use effective contraception while receiving Kadcyla and for 7 months following the last dose. Male patients or their female partners should also use effective contraception.

Anthracyclines must not be given in combination with, or within 6 months of last dose of, Kadcyla.

References

- Summary of Product Characteristics Kadcyla (Roche) accessed 9 March 2017 via www.medicines.org.uk
- Verma S. et al. Trastuzumab Emtansine for HER2-Positive Advanced Breast Cancer. N Engl J Med 2012; 367(19): 1783-91

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Date: April 2017